Cochrane Library

Cochrane Database of Systematic Reviews

Sedation for moderate-to-severe traumatic brain injury in adults: a network meta-analysis (Protocol)

Burry L, Dryden L, Rose L, Williamson DR, Adhikari NKJ, Turgeon AF, Golan E, Dewhurst N, Fergusson DA, Hutton B, Mehta S

Burry L, Dryden L, Rose L, Williamson DR, Adhikari NKJ, Turgeon AF, Golan E, Dewhurst N, Fergusson DA, Hutton B, Mehta S.
Sedation for moderate-to-severe traumatic brain injury in adults: a network meta-analysis.
Cochrane Database of Systematic Reviews 2017, Issue 4. Art. No.: CD012639.
DOI: 10.1002/14651858.CD012639.

www.cochranelibrary.com

WILEY

TABLE OF CONTENTS

[Intervention Protocol]

Sedation for moderate-to-severe traumatic brain injury in adults: a network meta-analysis

Lisa Burry[1], Lindsay Dryden[2], Louise Rose[3], David R Williamson[4], Neill KJ Adhikari[5], Alexis F Turgeon[6], Eyal Golan[7], Norman Dewhurst[8], Dean A Fergusson[9], Brian Hutton[10], Sangeeta Mehta[11]

[1]Department of Pharmacy, Mount Sinai Hospital, Leslie Dan Faculty of Pharmacy, University of Toronto, Toronto, Canada. [2]Leslie Dan Faculty of Pharmacy, University of Toronto, Toronto, Canada. [3]Lawrence S. Bloomberg Faculty of Nursing, University of Toronto, Toronto, Canada. [4]Faculty of Pharmacy / Department of Pharmacy, Université de Montréal / Höpital du Sacré-Coeur de Montréal, Montreal, Canada. [5]Interdepartmental Division of Critical Care, University of Toronto, Toronto, Canada. [6]Department of Anesthesiology and Critical Care Medicine, Division of Critical Care Medicine, and Population Health and Optimal Health Practices Research Unit (Trauma - Emergency - Critical Care Medicine), CHU de Québec - Université Laval Research Center, CHU de Québec - Université Laval, Université Laval, Quebec City, Canada. [7]Department of Medicine, University Health Network, Toronto, Canada. [8]Department of Pharmacy, St. Michaels Hospital, Toronto, Canada. [9]Clinical Epidemiology Program, Ottawa Hospital Research Institute, Ottawa, Canada. [10]Knowledge Synthesis Group, Ottawa Hospital Research Institute, Ottawa, Canada. [11]Interdepartmental Division of Critical Care Medicine, Mount Sinai Hospital, University of Toronto, Toronto, Canada

Contact address: Lisa Burry, Department of Pharmacy, Mount Sinai Hospital, Leslie Dan Faculty of Pharmacy, University of Toronto, 600 University Avenue, Room 18-377, Toronto, ON, M5G 1X5, Canada. lburry@mtsinai.on.ca.

Editorial group: Cochrane Injuries Group.
Publication status and date: New, published in Issue 4, 2017.

Citation: Burry L, Dryden L, Rose L, Williamson DR, Adhikari NKJ, Turgeon AF, Golan E, Dewhurst N, Fergusson DA, Hutton B, Mehta S. Sedation for moderate-to-severe traumatic brain injury in adults: a network meta-analysis. *Cochrane Database of Systematic Reviews* 2017, Issue 4. Art. No.: CD012639. DOI: 10.1002/14651858.CD012639.

ABSTRACT

This is a protocol for a Cochrane Review (Intervention). The objectives are as follows:

To assess the effects of sedative, analgesic, and anaesthetic drugs on neurological outcomes in adults with moderate-to-severe TBI.

BACKGROUND

Description of the condition

Traumatic brain injury (TBI) is a leading cause of morbidity and mortality worldwide (CDC 2014). Trauma to the brain is classified as primary or secondary, and both types of injury can occur simultaneously as a continuum of overlapping neurological insults. Primary injury occurs with the initial trauma and can result in diffuse or localised injury, cerebral oedema, and intracranial haemorrhage, any of which can raise intracranial pressure (ICP), reduce cerebral perfusion pressure (CPP), or worsen cerebral ischaemia. Secondary injury occurs as a result of additional neurological insults from hypercapnoea, hypoxia, systemic hypotension, and raised ICP. Both primary and secondary brain injuries are associated with increased mortality, as well as long-term neurological morbidity (e.g. impairments in memory and reasoning, as well as behavioural and mental health disorders) (Brain Trauma Foundation 2007;

Chowdhury 2014; Ribbers 2010; Roberts 2011).

Description of the intervention

Sedatives and opioids are commonly used in the intensive care unit (ICU) to facilitate the use of life-supporting technologies (e.g. support ventilator synchrony), mitigate pain, and reduce anxiety and agitation (Arroliga 2005; Barr 2013; Burry 2014). While these drugs facilitate tolerance of the ICU environment, there are notable complications associated with their use. Careful selection of drug(s) and method of titration are endorsed by the Society of Critical Care Medicine given the accumulating data indicating suboptimal sedation practices may prolong mechanical ventilation, and increase delirium and long-term cognitive impairment (Arabi 2007; Barr 2013; Brattebo 2004; Brook 1999; Girard 2008; Kollef 1998; Kress 2000; Kress 2003; Pandharipande 2007; Strøm 2010). In addition to the traditional application of sedation in the ICU, drugs may be administered in people with TBI, especially in the acute phase following the initial injury. Sedatives and opioids, as well as anaesthetics, are often used in the TBI population to control ICP, reduce metabolic rate (e.g. cerebral metabolic rate of oxygen ($CMRO_2$)), manage or prevent seizures, and improve mechanical ventilator synchrony to achieve optimal arterial blood gas (partial pressure of carbon dioxide in arterial blood ($PaCO_2$) and partial pressure of oxygen in arterial blood (PaO_2)) concentrations (Brain Trauma Foundation 2017; Kelly 1999; Skoglund 2013).
Unfortunately, many of these drugs are associated with adverse effects (e.g. haemodynamic instability) that may consequently increase the risk of secondary brain injury (Roberts 2012; Urwin 2004). In addition, the long-term effects of these agents on cognitive outcomes are unknown. An ideal sedative for people with acute severe TBI would: 1. confer neuroprotection (e.g. ICP control and reduction in $CMRO_2$) without compromising systemic haemodynamics or causing adverse effects (e.g. propofol infusion syndrome); 2. permit frequent neurological assessment; 3. address specific symptoms of agitation, anxiety, ventilator dyssynchrony, and pain; and 4. improve clinical outcomes (e.g. neurological function, duration of mechanical ventilation, and survival) (Barr 2013; Brain Trauma Foundation 2007; Chowdhury 2014; Flower 2012; Urwin 2004).

How the intervention might work

Various sedative, opioid, and anaesthetic agents are used in the acute management of moderate-to-severe TBI. These drugs can be used in the traditional context of sedation and analgesia, but can also be employed for their neuroprotective properties (e.g. reduction of cerebral metabolic rate and oxygen consumption). Sedatives, opioids, and anaesthetics may, therefore, play a role in the optimisations of patient care, improving both short- and long-term (e.g. neurological function) outcomes. Unfortunately, the majority of these drugs can also cause important adverse effects (e.g. systemic hypotension, bradycardia) especially when administered at higher doses to achieve deep sedation. Propofol, benzodiazepines, and barbiturates are thought to act as neuroprotectants through their modulation of gabaminergic transmission, where they reduce cerebral blood flow (CBF), $CMRO_2$, and ICP (Urwin 2004). The $alpha_2$–adrenergic agonist dexmedetomidine reduces CBF and ICP, and ketamine is an antagonist of N-methyl-D-aspartate (NMDA) receptors, where it decreases cerebral glutamate activity. Lastly, opioids modulate the mu receptor where they affect pain, but they can also be used for their sedating properties. Many of the aforementioned drugs confer broad therapeutic effects. For example, ketamine can be used for analgesia, and propofol, benzodiazepines, and barbiturates have anticonvulsant properties.

Why it is important to do this review

The World Health Organization (WHO) has predicted TBI will surpass many illnesses, including cancer and cardiovascular disease, as the major cause of death and disability by 2020 (Mathers 2006). In the US, more than 1.4 million people experience a TBI each year, with 50,000 reported deaths (Richmond 2011). The economic burden of TBI is considerable: in the US, the estimated combined direct and indirect economic cost of TBI in 2010 was estimated at USD 76.5 billion (CDC 2014).
The Society of Critical Care Medicine 2013 Pain, Agitation and Delirium Guidelines recommend a light level of sedation using either protocolised sedation or daily sedation interruption in adults in the ICU, as this is associated with improved clinical outcomes (Barr 2013). However, these guidelines do not provide direction on general sedation practice for people with moderate-to-severe TBI. The Brain Trauma Foundation guidelines for management of severe TBI suggest high-dose barbiturates may be necessary to control elevated ICP refractory to standard drug or surgical interventions while ensuring haemodynamic stability (Brain Trauma Foundation 2017). The guidelines also caution against the use of high-dose propofol for ICP management given the associated adverse events (e.g. metabolic acidosis, rhabdomyolysis) and morbidity.
In addition to the overall sparsity of resources to guide the clinical management of moderate-to-severe TBI, an important limitation of existing reviews and guidelines is that interventions were considered in isolation and only direct evidence from head-to-head comparisons (i.e. employing pair-wise meta-analytic techniques) was used (Brain Trauma Foundation 2017; Gu 2014; Roberts 2011; Roberts 2012). Given this limitation, we propose a novel synthesis of the evidence using a network meta-analysis (NMA), a powerful statistical approach that enables the inclusion of both direct and indirect evidence in a multi-treatment analytical framework (Catala-Lopez 2014; Ioannidis 2009; Lu 2004).
An NMA framework will enable the determination of the relative efficacy and safety of sedative, analgesic, and anaesthetic drugs

that may not have been previously compared head-to-head in published trials or reviews. This is particularly important given the growing use of new sedative agents (e.g. dexmedetomidine) in the TBI population (Tang 2011; Wang 2013). The findings of this NMA will highlight the comparative benefits and harms of each intervention and permit their ranking according to effectiveness and acceptability. An updated knowledge synthesis in this area will inform treatment algorithms and provide guidance to clinicians, ultimately guiding future research protocols and knowledge translation opportunities.

OBJECTIVES

To assess the effects of sedative, analgesic, and anaesthetic drugs on neurological outcomes in adults with moderate-to-severe TBI.

METHODS

Criteria for considering studies for this review

Types of studies

We will include randomised controlled trials (RCTs), including those of open-label design. We will exclude crossover studies and studies examining the effects of sedatives for procedural purposes specifically (e.g. intubation). We will also exclude studies of prehospital care of people with TBI. We will only include trials that were prospectively registered, unless the final report was published before 2010.

Types of participants

We will include studies that enrol adults aged over 16 years diagnosed with moderate-to-severe TBI.

Types of interventions

We will include studies comparing any sedative, analgesic, or anaesthetic to an alternative drug of either the same or different class, or to placebo, for the management of moderate-to-severe TBI. Interventions will include alpha-2-agonists (e.g. dexmedetomidine), anaesthetics (e.g. volatile gases), benzodiazepines (e.g. midazolam), non-benzodiazepine sedatives (e.g. propofol), barbiturates (e.g. pentobarbital), and opioids (e.g. fentanyl). For this analysis, drug dose, duration of use, and route of administration will not be restricted. Each drug class will have an individual node in the NMA framework. Additional interventions identified in the search will be considered in the framework if the study meets prespecified inclusion criteria.

Types of outcome measures

Primary outcomes

1. Neurological outcome (Glasgow Outcome Scale (GOS) or the Glasgow Outcome Scale Extended (GOSe), measured at three and six months).

Secondary outcomes

1. Cerebral haemodynamic measures (i.e. ICP, CPP) in the acute phase (i.e. 24 to 72 hours, related to the primary TBI injury and the main reason for administering sedation).
2. Cerebral oxygenation ($CMRO_2$) in the acute phase (i.e. 24 to 72 hours).
3. Duration of mechanical ventilation (days).
4. ICU and hospital length of stay (days).
5. Mortality (e.g. one, three, six, or 12 months, or as reported by study authors).
6. Adverse events (e.g. hypotension, bradycardia).

Search methods for identification of studies

To reduce publication and retrieval bias, we will not restrict studies based on language, date, or status of publication.

Electronic searches

The Cochrane Injuries Group Information Specialist will search the following:

1. Cochrane Injuries Group specialised register (present version);
2. the Cochrane Library (www.cochranelibrary.com/) (latest issue);
3. Ovid MEDLINE(R), Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid OLDMEDLINE(R) (1946 to present);
4. Embase Classic + Embase (OvidSP) (1947 to present);
5. PubMed (www.ncbi.nlm.nih.gov/pubmed/) (present);
6. ISI Web of Science: Science Citation Index Expanded (SCI-EXPANDED) (1970 to present);
7. ISI Web of Science: Conference Proceedings Citation Index-Science (CPCI-S) (1990 to present);
8. LILACS (lilacs.bvsalud.org/) (present);
9. PROSPERO (www.crd.york.ac.uk/prospero/search.asp) (present);
10. Clinicaltrials.gov (www.clinicaltrials.gov);

11. WHO International Clinical Trials Registry Platform (apps.who.int/trialsearch/).

We will adapt the MEDLINE strategy (Appendix 1) as necessary for other databases.

We will use the search filters and a modified version of the "Cochrane Highly Sensitive Search Strategies" for identifying RCTs in MEDLINE and Embase (Lefebvre 2011).

Searching other resources

We will perform a search of grey literature databases and websites using resources listed in CADTH's Grey Matters (www.cadth.ca/en/resources/finding-evidence-is/grey-matters).

We will handsearch the abstracts from the annual scientific meetings of relevant groups (e.g. Society of Critical Care Medicine, World Congress on Brain Injury, Neurocritical Care Society, European Society of Intensive Care Medicine) from the five years prior to the review's search date.

We will also search for unpublished and ongoing trials at www.who.int/trialsearch and ClinicalTrials.gov using the term "traumatic brain injury."

We will handsearch the reference lists of all screened and included studies, as well as any reviews published in the five years prior to the review's search date focusing on sedation in people with TBI for identification of potential additional studies.

Data collection and analysis

Selection of studies

Two authors (LD, LB) will develop and pilot the study screening form (Appendix 2) on five studies to ensure its ability to accurately identify studies meeting inclusion criteria. Two authors (LD, LB) will use the study screening form to independently examine each title and abstract generated through the searches to identify eligible studies. We will refer any disagreements to a third independent author (AT), if needed. We will organize references in EndNote (EndNote 2014). This systematic review will adhere to best practice reporting guidelines using the PRISMA criteria (Moher 2009). A PRISMA-compliant flow diagram will demonstrate the search and study selection process.

Data extraction and management

We will perform data extraction using a standardized electronic form developed by two authors (LD, LB) and piloted on three studies to ensure its ability to capture all relevant data. Pairs of authors (LR and DW; SM and EG; ND and NA) will independently extract the data using the standardized data extraction form.

We will extract data related to the following:

1. study design;
2. publication year and authors;
3. trial population (e.g. sample size, age, percentages of people with moderate and severe TBI in the sample);
4. interventions (i.e. sedative agent used, dose, duration of use, route of administration);
5. control or comparators;
6. selected outcomes.

We will also extract data on randomisation methods, allocation concealment, blinding, frequency and handling of missing data, adherence to intention-to-treat, and selective reporting of outcomes (Higgins 2011). Given our familiarity with the literature, we will not blind data extractors to the authors of included studies. All data extraction will be checked for accuracy, and any discrepancies will be resolved by an independent author (LD).

We are aware that all outcomes may not be reported in each trial. Whenever possible, if outcomes of interest have been omitted, we will attempt to contact the corresponding author(s) of eligible trials to obtain additional information. In the event that abstracts are identified that present relevant data, we will also endeavour to contact study authors directly for additional study details.

Assessment of risk of bias in included studies

Two authors (LR and DW; SM and EG; ND and NA) will independently assess risk of bias of included studies. Assessment of bias will be compared between authors, and one author (SM) will resolve discrepancies, if necessary.

These assessments will use a domain-based evaluation embedded in the data extraction form. We will use the Cochrane tool framework for assessing bias and include the following domains (Higgins 2011):

1. random sequence generation (i.e. selection bias);
2. allocation concealment (i.e. selection bias);
3. blinding of participants and personnel (i.e. performance bias);
4. blinding of outcomes assessment (i.e. detection bias);
5. incomplete outcome data (i.e. attrition bias);
6. selective reporting; and
7. other bias.

For each domain, we will assess the risk of bias as 'low,' 'high,' or 'unclear' risk. An 'unclear' assessment will be assigned if insufficient information is reported, or if the risk of bias is unknown despite attempts to contact a study author. Once the risk of bias is agreed upon, each study will be assigned to one of the following categories:

1. low risk of bias: describes studies where all domains are deemed to have 'low' risk of bias;
2. high risk of bias: describes studies where one or more domains are scored as 'no' indicating 'high' risk of bias; or
3. unclear risk of bias: describes studies where one or more domain was scored as 'unclear' risk or one domain was scored as 'high' risk of bias.

We will generate a risk of bias summary figure upon completion of these assessments.

Measures of treatment effect

For cerebral outcomes, we will meta-analyse between-group differences in the acute phase (i.e. 24 to 72 hours) (this acute period finding will be reported in the 'Summary of findings' table) if there are sufficient data for pooling. We will analyse functional outcome measure (e.g. GOS and GOSe) in a dichotomous manner. Favourable outcome measures will be defined as a GOS of 1 to 3 or a GOSe of 1 to 5, while unfavourable outcomes will be defined as a GOS of 4 or 5 or a GOSe of 6 to 8. Dichotomous outcomes will be expressed as risk ratios with 95% confidence intervals.
Risk ratio was selected over risk difference to measure the effects of binary outcomes due its superior consistency across a range of baseline risks (Deeks 2002). Continuous variables (e.g. length of ICU stay, duration of mechanical ventilation, ICP, CPP) will be assessed using a mean difference and odds ratios. If the data are skewed, these will be log transformed. We will consider two-sided $P \leq 0.05$ to be statistically significant.

Unit of analysis issues

We will use individual study participants in each trial arm as the unit of analysis.

Dealing with missing data

We will contact the study authors to request missing or additional data, or for clarification on how missing data were dealt with in a particular study.

Assessment of heterogeneity

If assessed outcomes lack data, or if studies are too clinically or methodologically (or both) heterogeneous to permit pooling of data, we will report data in a table format and summarize them qualitatively.
Where appropriate, we will assess for statistical heterogeneity using Chi^2 and I^2 tests. The Chi^2 test assesses whether the observed differences in results are compatible with chance alone. A low P value provides evidence of heterogeneity of intervention effects that is beyond chance ($P < 0.10$ will be significant) (Higgins 2003). Assessment of the I^2 statistic describes the percentage of variability in effect estimates that is due to data heterogeneity rather than chance (i.e. sampling error) (Higgins 2011). Studies also will be assessed for types and sources of heterogeneity, either clinical or methodological, when making the decision to pool data. Clinical heterogeneity will be assessed through examination of the type and dose of sedative, and use of rescue sedation. We will also assess for heterogeneity by performing analyses based on potential modifiers of treatment effect, including the severity of TBI and year of study publication.

Assessment of reporting biases

Reporting biases can occur due to an increased likelihood of positive trials (large or small) being published compared to negative trials. For comparisons where at least 10 studies are available, we will construct funnel plots in Review Manager 5 (RevMan 2014) to assess for possible publication bias (Egger 2007; Higgins 2011).

Data synthesis

We will conduct pair-wise meta-analyses for all outcomes and comparisons where three or more studies are available, using a random-effects model with the Der Simonian and Laird method. A random-effects model employs a more conservative approach than a fixed-effect model, as it considers the variability within a study as well as among studies (Higgins 2011).
We will perform NMA within a Bayesian framework by assuming a common heterogeneity parameter across all comparisons. We will perform analyses using WinBUGS software (version 1.4.3 MRC Biostatistics Unit, Cambridge, UK) through well-established methods (Lu 2006; Salanti 2011). We will adhere to the recommendations from the PRISMA-NMA for reporting identified findings including forest plots, and rank-o-grams (Hutton 2015).

Subgroup analysis and investigation of heterogeneity

We will perform the following subgroup analyses:

1. severity of TBI: (moderate (i.e. Glasgow Coma Score (GCS) 9 to 12) versus severe (i.e. GCS 3 to 8)).
2. indication for sedation (i.e. presence or absence of ICP).

Sensitivity analysis

We will perform a sensitivity analysis removing studies rated as high risk of bias. We will use trial sequential analysis methods to explore any statistically significant effect found where the outcome did not meet the expected sample size.

Presentation of main results

We will present each comparison and selected outcomes of the review using a 'Summary of findings' table (Schunëmann 2011a), including the following outcomes

1. neurological outcome as measured by GOS/GOSe (at three and six months);
2. ICP;
3. CPP;
4. duration of mechanical ventilation;
5. hypotension.

The 'Summary of findings' table will include an overall grading of the evidence using the principles of the GRADE system (tech.cochrane.org/revman/gradepro; Schunëmann 2011b). We will grade the quality of evidence for our selected outcomes as high, moderate, low, or very low, based on risk of bias, within study evidence directness, heterogeneity, precision of effect estimates, and publication bias. We will base the control event rates for the calculation of absolute risks on the number of events in the included studies.

ACKNOWLEDGEMENTS

We would like to acknowledge Deirdre Beecher and Sarah Dawson, Information Specialists with the Cochrane Injuries Group, for their assistance with the development of the search strategy for this review. We would also like to thank Dr Victoria McCredie, Intensivist at Toronto Western Hospital for input on the development of the methodology for this review. Lastly, we would like to thank Melanie Guenette, Research Co-ordinator, Department of Pharmacy, Mount Sinai Hospital, for her editorial assistance in the publication of this protocol.

This project was supported by the UK National Institute for Health Research, through Cochrane Infrastructure funding to the Cochrane Injuries Group. The views and opinions expressed are those of the authors and do not necessarily reflect those of the Systematic Reviews Programme, NIHR, NHS or the Department of Health.

REFERENCES

Additional references

Arabi 2007
Arabi Y, Haddad S, Hawes R, Moore T, Pillay M, Naidu B, et al. Changing sedation practices in the intensive care unit - protocol implementation, multifaceted multidisciplinary approach and teamwork. *Middle East Journal of Anesthesiology* 2007;**19**(2):429–47.

Arroliga 2005
Arroliga A, Frutos-Vivar F, Hall J, Esteban A, Apezteguia C, Soto L, et al. Use of sedatives and neuromuscular blockers in a cohort of patients receiving mechanical ventilation. *Chest* 2005;**128**(2):496–506.

Barr 2013
Barr J, Fraser GL, Puntillo K, Ely EW, Gelinas C, Dasta JF, et al. Clinical practice guidelines for the management of pain, agitation, and delirium in adult patients in the intensive care unit. *Critical Care Medicine* 2013;**41**(1): 263–306.

Brain Trauma Foundation 2007
Bratton SL, Chestnut RM, Ghajar J, McConnell Hammond FF, Harris OA, Hartl R, et al. Guidelines for the management of severe traumatic brain injury. XI. Anesthetics, analgesics, and sedatives. *Journal of Neurotrauma* 2007;**24**(Suppl 1):S71–6.

Brain Trauma Foundation 2017
Carney N, Totten AM, O'Reilly CBS, Ullman JS, Hawryluk GWJ, Bell MJ, et al. Guidelines for the management of severe traumatic brain injury. *Neurosurgery* 2017;**80**(1): 6–15.

Brattebo 2004
Brattebo G, Hofoss D, Flaatten H, Muri AK, Gjerde S, Plsek PE. Effect of a scoring system and protocol for sedation on duration of patients' need for ventilator support in a surgical intensive care unit. *Quality and Safety in Health Care* 2004;**13**(3):203–5.

Brook 1999
Brook AD, Ahrens TS, Schaiff R, Prentice D, Sherman G, Shannon W, et al. Effect of a nursing-implemented sedation protocol on the duration of mechanical ventilation. *Critical Care Medicine* 1999;**27**(12):2609–15.

Burry 2014
Burry LD, Williamson DR, Perreault MM, Rose L, Cook DJ, Ferguson ND, et al. Analgesic, sedative, antipsychotic, and neuromuscular blocker use in Canadian intensive care units: a prospective, multicentre, observational study. *Canadian Journal of Anesthesia* 2014;**61**(7):619–30.

Catala-Lopez 2014
Catala-Lopez F, Tobias A, Cameron C, Moher D, Hutton B. Network meta- analysis for comparing treatment effects of multiple interventions: an introduction. *Rheumatology International* 2014;**34**(11):1489–96.

CDC 2014
Centers for Disease Control and Prevention. Injury prevention and control: traumatic brain injury, 2014. www.cdc.gov/TraumaticBrainInjury/ (accessed prior to 9 April 2017).

Chowdhury 2014
Chowdhury T, Kowalski S, Arabi Y, Dash HH. General intensive care for patients with traumatic brain injury: an update. *Saudi Journal of Anaesthesia* 2014;**8**(2):256–63.

Deeks 2002
Deeks JJ. Issues in the selection of a summary statistic for meta-analysis of clinical trials with binary outcomes. *Statistics in Medicine* 2002;**21**(11):1575–600.

Egger 2007
Egger M, Smith GD, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997;**315**(7109):629–34.

EndNote 2014 [Computer program]
EndNote. Version X6. Carlsbad (CA): Thomson Reuters, 2014.

Flower 2012
Flower O, Hellings S. Sedation in traumatic brain injury. *Emergency Medicine International* 2012;**2012**:1–11.

Girard 2008
Girard TD, Kress JP, Fuchs BD, Thomason JWW, Schweickert WD, Pun BT, et al. Efficacy and safety of a paired sedation and ventilator weaning protocol for mechanically ventilated patients in intensive care (Awakening and Breathing Controlled trial): a randomised controlled trial. *Lancet* 2008;**371**(9607):126–34.

Gu 2014
Gu JW, Yang T, Kuang YQ, Huang HD, Kong B, Shu HF, et al. Comparison of the safety and efficacy of propofol with midazolam for sedation of patients with severe traumatic brain injury: a meta-analysis. *Journal of Critical Care* 2014; **29**(2):287–90.

Higgins 2003
Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003;**327** (7414):557–60.

Higgins 2011
Higgins JP, Altman DG, Gotzsche PC, Juni P, Moher D, Oxman AD, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ* 2011;**343**: d5928.

Hutton 2015
Hutton B, Salanti G, Caldwell DM, Chaimani A, Schmid CH, Cameron C, et al. The PRISMA extension statement for reporting of systematic reviews incorporating network meta-analyses of health care interventions: checklist and explanations. *Annals of Internal Medicine* 2015;**162**(11): 777–84.

Ioannidis 2009
Ioannidis JP. Integration of evidence from multiple meta-analyses: a primer on umbrella reviews, treatment networks and multiple treatments meta-analyses. *Canadian Medical Association Journal* 2009;**181**(8):488–93.

Kelly 1999
Kelly DF, Goodale DB, Williams J, Herr DL, Chappell ET, Rosner MJ, et al. Propofol in the treatment of moderate and severe head injury: a randomized, prospective double-blinded pilot trial. *Journal of Neurosurgery* 1999;**90**(6): 1042–52.

Kollef 1998
Kollef MH, Levy NT, Ahrens TS, Schaiff R, Prentice D, Sherman G. The use of continuous i.v. sedation is associated with prolongation of mechanical ventilation. *Chest* 1998; **114**(2):541–8.

Kress 2000
Kress JP, Pohlman AS, O'Connor MF, Hall JB. Daily interruption of sedative infusions in critically ill patients undergoing mechanical ventilation. *New England Journal of Medicine* 2000;**342**(20):1471–7.

Kress 2003
Kress JP, Gehlbach B, Lacy M, Pliskin N, Pohlman AS, Hall JB. The long-term psychological effects of daily sedative interruption on critically ill patients. *American Journal Respiratory Critical Care Medicine* 2003;**168**(12):1457–61.

Lefebvre 2011
Lefebvre C, Manheimer E, Glanville J. Chapter 6: Searching for studies. In: Higgins JPT, Green S, editor(s). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from handbook.cochrane.org.

Lu 2004
Lu G, Ades AE. Combination of direct and indirect evidence in mixed treatment comparisons. *Statistics in Medicine* 2004;**23**(20):3105–24.

Lu 2006
Lu G, Ades A. Assessing evidence inconsistency in mixed treatment comparisons. *Journal of American Statistical Association* 2006;**101**(474):447–59.

Mathers 2006
Mathers CD, Loncar D. Projections of global mortality and burden of disease from 2002 to 2030. *PLoS Medicine* 2006; **3**(11):e442.

Moher 2009
Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Medicine* 2009;**6**(7):e1000097.

Pandharipande 2007
Pandharipande PP, Pun BT, Herr DL, Maze M, Girard TD, Miller RR. Effect of sedation with dexmedetomidine vs lorazepam on acute brain dysfunction in mechanically ventilated patients: the MENDS randomized controlled trial. *JAMA* 2007;**298**(22):2644–53.

RevMan 2014 [Computer program]
The Nordic Cochrane Centre, The Cochrane Collaboration. Review Manager (RevMan). Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014.

Ribbers 2010
Ribbers G. Brain injury: long term outcome after traumatic brain injury, 2010. International Encyclopedia of Rehabilitation. cirrie.buffalo.edu/encyclopedia/en/article/ 338/ (accessed prior to 9 April 2017).

Richmond 2011
Richmond R, Aldaghlas TA, Burke C, Rizzo AG, Griffen M, Pullarkat R. Age: is it all in the head? Factors influencing mortality in elderly patients with head injuries. *Journal of Trauma* 2011;**71**(1):E8–11.

Roberts 2011
Roberts DJ, Hall RI, Kramer AH, Robertson HL, Gallagher CN, Zygun DA. Sedation for critically ill adults with severe traumatic brain injury: a systematic review of randomized controlled trials. *Critical Care Medicine* 2011;**39**(12): 2743–51.

Roberts 2012
Roberts I, Sydenham E. Barbiturates for acute traumatic brain injury. *Cochrane Database of Systematic Reviews* 2012, Issue 12. [DOI: 10.1002/14651858.CD000033.pub2]

Salanti 2011
Salanti G, Ades AE, Ioannidis JP. Graphical methods and numerical summaries for presenting results from multiple-treatment meta-analysis: an overview and tutorial. *Journal of Clinical Epidemiology* 2011;**64**(2):163–71.

Schunëmann 2011a
Schunëmann H, Oxman A, Higgins J, Vist G, Glasziou P, Guyatt G. Chapter 11: Presenting results and Summary of finding tables. In: Higgins JP, Green S, editor(s). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from handbook.cochrane.org.

Schunëmann 2011b
Schunëmann H, Oxman A, Vist G, Higgins J, Deeks J, Glasziou P. Chapter 12: Interpreting results and drawing conclusions. In: Higgins JP, Green S, editor(s). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from handbook.cochrane.org.

Skoglund 2013
Skoglund K, Enblad P, Marklund N. Monitoring and sedation differences in the management of severe head injury and subarachnoid hemorrhage among neurocritical care centers. *Journal of Neuroscience Nursing: Journal of the American Association of Neuroscience Nurses* 2013;**45**(6): 360–8.

Strøm 2010
Strøm T, Martinussen T, Toft P. A protocol of no sedation for critically ill patients receiving mechanical ventilation: a randomised trial. *Lancet* 2010;**375**(9713):475–80.

Tang 2011
Tang JF, Chen PL, Tang EJ, May TA, Stiver SI. Dexmedetomidine controls agitation and facilitates reliable, serial neurological examinations in a non-intubated patient with traumatic brain injury. *Neurocritical Care* 2011;**15**(1): 175–81.

Urwin 2004
Urwin SC, Menon DK. Comparative tolerability of sedative agents in head-injured adults. *Drug Safety* 2004;**27**(2): 107–33.

Wang 2013
Wang X, Ji J, Fen L, Wang A. Effects of dexmedetomidine on cerebral blood flow in critically ill patients with or without traumatic brain injury: a prospective controlled trial. *Brain Injury* 2013;**27**(13-14):1617–22.

* *Indicates the major publication for the study*

APPENDICES

Appendix 1. Search strategy

Ovid MEDLINE(R), Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid OLDMEDLINE(R) (1946 to present)

1. exp Craniocerebral Trauma/ or exp Cerebrovascular Trauma/
2. (TBI or mTBI or sTBI or ((trauma* or mild* or moderate* or severe* or acquired) and (brain injur* or brain trauma* or head injur* or head trauma*))).ti,ab,kf.
3. *Multiple Trauma/
4. Glasgow Coma Scale/ or Glasgow Outcome Scale/
5. (Glasgow adj (coma or outcome) adj (scale* or score*)).ab,ti,kf.
6. (injur* or trauma* or damag* or wound* or fractur* or contusion* or haematoma* or hematoma* or haemorrhag* or hemorrhag* or pressur* or hypertensi* or lesion* or destruction* or oedema* or edema* or contusion* or concus*).ti,ab,kf.
7. (4 or 5) and 6
8. ((mild* or moderate* or severe*) adj5 (unconscious* or coma* or concuss*) adj3 (injur* or trauma* or damag* or wound* or fracture* or contusion* or haematoma* or hematoma* or haemorrhag* or hemorrhag* or pressur* or hypertensi*)).ti,ab,kf.
9. ((mild* or moderate* or severe*) adj5 (head or crani* or cerebr* or capitis or brain* or forebrain* or skull* or hemispher* or intra cran* or inter cran* or intracran* or intercran*) adj3 (injur* or trauma* or damag* or lesion* or wound* or destruction* or oedema* or edema* or contusion* or concus* or fracture* or pressure or hypertensi*)).ab,ti,kf.
10. (neurprotect* and ((head or crani* or cerebr* or capitis or brain* or forebrain* or skull* or hemispher* or intra cran* or inter cran* or intracran* or intercran*) adj3 (injur* or trauma* or damag* or lesion* or wound* or destruction* or oedema* or edema* or contusion* or concus* or fracture* or pressure or hypertension))).ab,ti,kf.

11. (subarachnoid h?emorrhage or tSAH).ti,ab,kf.
12. ((midbrain or mid brain) adj syndrome).ti,ab,kf.
13. diffuse axonal injur*.ti,ab,kf.
14. (or/1-3,7,8-13)
15. Conscious Sedation/
16. (sedative* or sedation).ti,ab,kf.
17. exp Adrenergic alpha-2 Receptor Agonists/
18. (Brimonidine or Clonidine or Dexmedetomidine or MPV-1440 or Guanabenz or Guanfacine or Medetomidine or Methyldopa or Xylazine).ti,ab,kf,rn.
19. exp "Hypnotics and Sedatives"/
20. (Propofol or Lidocaine or Tetracaine or Etomidate).ti,ab,kf,rn,sh.
21. (Ketamin* or Amantadin* or Atomoxetin* or Dextromethorphan or GLYX 13 or "MK 0657" or Lanicemin* or AZD6765 or Memantin* or Quinolin or Rellidep or Riluzol or Tramadol or ETS6103 or N Methyl D Aspartate or NMDA or NRX 1074 or Kainite or Gavestinel or GV150526).ti,ab,kf,rn,sh.
22. (Barbiturat* or Amobarbital or Barbital or Hexobarbital or Mephobarbital or Methohexital or Murexide or Pentobarbital or Phenobarbital or Primidone or Secobarbital or Thiobarbiturate* or Thiamylal or Thiopental or Thiopentobarbital* or Thiopentone or Penthiobarbital).ti,ab,kf,rn,sh.
23. (Benzodiazepin* or BZD or Abecarnil or Adinazolam or Alprazolam or Arfendazam or Bentazepam or Bretazenil or Bromazepam or Brotizolam or Camazepam or Chlordiazepoxide or Chlordesmethyldiazepam or Cinolazepam or Clobazam or Clonazepam or Clorazepate or Chlorazepate or Clotiazepam or Cloxazolam or Delorazepam or Demoxepam or Desmethyldiazepam or Desoxydemoxepam or Devazepide or Diazepam or Doxefazepam or Estazolam or ethyl loflazepate or CM 6912 or Etizolam or Fludiazepam or Flunitrazepam or Flurazepam or dealkylflurazepam or Flutoprazepam or Fosazepam or Gidazepam or Girisopam or Halazepam or Haloxazolam or Ketazolam or Loflazepate or Loprazolam or Lorazepam or Lormetazepam or Meclonazepam or Medazepam or Metaclazepam or Mexazolam or Midazolam or Nerisopam or Nimetazepam or Nitrazepam or Norchlordiazepoxide or Norclobazam or Nordazepam or Norfludiazepam or Norflunitrazepam or Oxazepam or WY 3498 or Oxazolam or Phenazepam or Pinazepam or Prazepam or Premazepam or Propazepam or Quazepam or Ripazepam or Serazepine or Sograzepide or Talampanel or Tarazepide or Temazepam or Tetrazepam or Tofisopam or Triazolam or Zolazepam or Zaleplon or Zolpidem or Zopiclone or Eszopiclone or Z Drug*).ti,ab,kf,rn,sh.
24. (Azaperone or Bromisovalum or Chloral hydrate or Chloralose or Chlormethiazole or Diphenhydramine or Ethchlorvynol or Etomidate or Etorphine or Glutethimide or Medetomidine or Meprobamate or Methapyrilene or Methaqualone or Paraldehyde or Xylazine).ti,ab,kf,rn,sh.
25. exp Narcotics/
26. exp Analgesics, Opioid/
27. (Alfentanil or Fentanyl or Remifentan* or Sufentanil or Hydromorphone or Dihydromorphinone or Morphine or Opiate* or Opioid*).ti,ab,kf,rn,sh.
28. or/15-27
29. randomi?ed.ab,ti.
30. randomized controlled trial.pt.
31. controlled clinical trial.pt.
32. placebo.ab.
33. clinical trials as topic.sh.
34. randomly.ab.
35. trial.ti.
36. Comparative Study/
37. or/29-36
38. (animals not (humans and animals)).sh.
39. 37 not 38
40. (14 and 28 and 39)

Appendix 2. Study screening form

Review author Initials	Review date: / / (dd/mm/yy)		
Primary author			
Citation (title, journal, year, vol, pg)			
Level of review	Title and abstract	Full text	

STUDY SELECTION				**STUDY SELEC**
Study type	RCT or non-randomized study	Yes	No	
Population	Majority (≥ 50%) of study participants are ≥ 16 years old with moderate-to-severe TBI (GCS = 3-12 or documented traumatic head/brain injury)	Yes	No	
	Study participants received care in an intensive care setting (critical care or intensive care of any specialty)	Yes	No	
Intervention	Pharmacological sedation	Yes	No	
	Study does not use intervention exclusively or rapid-sequence intubation	Yes	No	
Comparison (only for RCTs)	Alternative pharmacological sedation or placebo	Yes	No	
Decision	INCLUDE	EXCLUDE		
Primary reason for exclusion	Study type			
	Population			Population
	Intervention			Intervention
	Comparison			Comparison
GCS: Glasgow Coma Score; RCT: randomized controlled trial; TBI: traumatic brain injury				GCS: Glasgow controlled trial;

CONTRIBUTIONS OF AUTHORS

Drafting of protocol: LB; LD; LR; DW; NA; AT; EG; ND; DF; BH; and SM.

DECLARATIONS OF INTEREST

LB: none known.

LD: none known.

LR: none known.

DW: has received an educational research grant from Hospira (now Pfizer), the company that makes Precedex (dexmedetomidine).

NA: none known.

AT: none known.

EG: none known.

ND: none known.

DF: none known.

BH: none known.

SM: none known.

SOURCES OF SUPPORT

Internal sources

- None, Other.

External sources

- No sources of support supplied